National Research Council Report on Scientific Evidence Pertaining to the Relationship Between Formaldehyde Exposure and Leukemia: Implications for the National Toxicology Program's Listing of Formaldehyde in the 12th Report on Carcinogens

Prepared on behalf of:
The American Chemistry Council
Washington, DC

Prepared by:
ENVIRON International Corporation
Arlington, Virginia
Amherst, Massachusetts
Boston, Massachusetts
Monroe, Louisiana

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Acknowledgements

ENVIRON International Corporation (ENVIRON) conducted this review and prepared these comments on behalf of the American Chemistry Council. The ENVIRON team included:

Annette M. Shipp, PhD
P. Robinan Gentry, PhD
Cynthia Van Landingham, MS
Tracy McDonald, BS
1900 N 18th Street, Suite 804
Monroe, LA 71201

Joseph Rodricks, PhD
Duncan Turnbull, D Phil
4300 N Fairfax Drive, Suite 300
Arlington, Virginia 22203

Kenneth Mundt, PhD
Renika Montgomery MPH
28 Amity Street, Suite 2A
Amherst, Massachusetts 01002

Diane J. Mundt, PhD
99 Summer Street, Room 2010
Boston, MA 02110

ENVIRON wishes to acknowledge the following external experts with whom ENVIRON consulted on key scientific issues:

Richard Albertini, PhD
Research Professor Emeritus
University of Vermont

Philip Cole, MD, Dr PH
Department of Epidemiology
School of Public Health
University of Alabama at Birmingham

Richard D. Irons, PhD
Cinpathogen International, LLC
Boulder, Colorado

Jack Mandel, PhD, MPH
Exponent, Inc.
Menlo Park, California

Gary M. Marsh, PhD, FACE
Graduate School of Public Health
Department of Biostatistics
Center for Occupational Biostatistics & Epidemiology
University of Pittsburgh

James Swenberg, DVM
Kenan Distinguished Professor
Environmental Sciences and Engineering
Director of Curriculum in Toxicology
University of North Carolina

Michael Thirman, MD
Associate Professor of Medicine
University of Chicago Medical Center

Summary

The National Research Council (NRC) of the National Academies was charged with conducting an independent scientific review of the United States Environmental Protection Agency's (EPA's) draft Integrated Risk Information System (IRIS) assessment of formaldehyde. On April 8, 2011, the NRC released a report by a committee of scientists recognized as experts in most of the scientific disciplines necessary to evaluate the human health hazards of formaldehyde. This independent committee reviewed and commented on EPA's draft IRIS assessment of the relevant scientific literature, and has significantly challenged EPA's evaluation of the possible relationship between formaldehyde exposure and human leukemia. The committee concluded that EPA's claims that formaldehyde causes leukemia, myeloid leukemia or related hematopoietic cancers are not supported in EPA's assessment. The committee noted that EPA's preliminary conclusion that a causal relationship is supported in the data appeared to be "subjective' in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The absence of such a framework was judged by the committee as troublesome, given that the available scientific evidence on the question is very weak.

As emphasized by the NRC committee:

> ***"…the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data."*** ***(NRC 2011, p. 8)***

The NRC committee stated that the epidemiologic data were limited by:

> ***"…uncertainties of exposure assessment, possible confounding by other pollutants, and reliance on mortality data rather than incidence data….".*** ***(NRC 2011, p. 83)***

The National Toxicology Program (NTP) also has been reviewing the scientific data for formaldehyde in preparation for a listing decision in the 12th Report on Carcinogens (RoC). EPA and the NTP have had available, reviewed and relied upon the same studies, reports and underlying data in conducting their respective hazard evaluations of the possible relationship between formaldehyde exposure and leukemia and other lymphohematopoietic malignancies. ***Therefore, the NRC committee's review of and conclusions concerning the draft EPA IRIS report are, with respect to lymphohematopoietic malignancies (including myeloid leukemia), directly applicable to the NTP's own review and conclusions – precisely because the draft EPA and NTP reports involve the same studies and data sets***.

The NRC committee's opinion was that EPA's review of the scientific literature as presented in the draft IRIS assessment does not provide a sufficient scientific basis for concluding that there is a causal link between formaldehyde exposure and leukemia. The NRC committee's conclusions concerning EPA's assessment of leukemia apply as well to application of the "listing criteria" for formaldehyde in the NTP's 12th RoC. ***In particular, there is no reasonable scientific basis for the NTP to conclude that formaldehyde should be listed in the 12th RoC as being either "known" or "reasonably anticipated" to cause myeloid leukemia or any other lymphohematopoietic malignancy***.

The NRC committee's review of the draft IRIS formaldehyde assessment agreed that the EPA criteria for causality were satisfied for formaldehyde and nasopharyngeal cancer (NPC) "on the basis of the combination of the epidemiologic findings with experimental data and mechanistic data on

formaldehyde" (NRC, 2011, p. 63). However, the epidemiologic evidence alone was not sufficient and, based on the NTP listing criteria, would not satisfy the NTP's definition of a "known" human carcinogen.

Therefore, in light of the NRC review, the listing of formaldehyde as "reasonably anticipated to be a human carcinogen," as classified by the NTP in the 11th RoC and previous RoC assessments, also would be the appropriate designation in the 12th RoC. This designation should be based solely, as in the 11th RoC, on evidence that exposure to formaldehyde shows limited evidence in humans of increased incidences of nasopharyngeal cancer in exposed workers, and an increased incidence of squamous cell carcinoma of the nasal cavity in rats exposed by inhalation. The existing scientific evidence does not support listing formaldehyde as either a "known" or "reasonably anticipated" human leukemogen according to the NTP listing criteria, and should not be advanced as such in the NTP's 12th RoC.

The following sections summarize the key scientific evidence and bases for conclusions discussed by the NRC committee, as they apply to the NTP's proposed listing of formaldehyde as a human carcinogen in the 12th RoC. ENVIRON and a team of external experts (noted above) previously evaluated this evidence, and reached conclusions consistent with the NRC committee's findings. The comments that we previously prepared and submitted to the NTP concerning the possible association between formaldehyde exposure and leukemia, in particular myeloid leukemia, are consistent with those expressed by the NRC committee.

Weight-of-Evidence Evaluation

The NRC committee stated that EPA's conclusion of a causal relationship between formaldehyde and lymphohematopoietic (LHP) cancer was "subjective" in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The absence of such a framework was judged by the NRC committee as problematic, given that the available scientific evidence on the question is very weak. As emphasized by the committee:

> ***"…there is no clearly articulated framework for establishing causation on the basis of the weight and strength of evidence. An*** a priori ***presentation of the study selection criteria (for example, quality of exposure assessment, control of confounding variables, and statistical power) is also missing. Both the framework and study selection criteria are critical for any determination of causation."*** ***(NRC 2011, p. 83)***

> ***"Because the draft IRIS assessment presents no causal framework explicitly, the committee considered the appropriateness of EPA's conclusions in the context of EPA's*** Guidelines for Carcinogen Risk Assessment ***(EPA 2005). The guidelines state that for a substance to be a known human carcinogen, there should be "convincing epidemiologic evidence of a causal association between human exposure and cancer" or, exceptionally, if all the following conditions are met: "(a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and (b) there is extensive evidence of carcinogenicity in animals, and (c) the model(s) of carcinogenic action and associated key precursor events have been identified in animals, and (d) there is strong evidence that the key precursor events that precede the***

cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information" (EPA 2005, p. 2-54)." *(NRC 2011, p. 63)*

"Numerous EPA guidelines are cited, but their role in the preparation of the assessment is not clear. In general, the committee found that the draft was not prepared in a consistent fashion; it lacks clear links to an underlying conceptual framework; and it does not contain sufficient documentation on methods and criteria for identifying evidence from epidemiologic and experimental studies, for critically evaluating individual studies, for assessing the weight of evidence, and for selecting studies for derivation of the RfCs and unit risk estimates." *(NRC 2011, pp. 3-4)*

"As a result, the conclusions appear to be based on a subjective view of all the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies of the epidemiologic data, the weak animal data, and the lack of mechanistic data." *(NRC 2011, p. 8)*

The NRC committee stated in several sections of its report that EPA did not define criteria for the evaluation of the strengths and weaknesses of the data nor the ability of data presented in studies to support conclusions reached; that is, according to the NRC committee, EPA did not conduct a weight-of-evidence analysis. The EPA guidelines for human health cancer assessment (EPA 2005) require a comprehensive weight-of-evidence analysis that must include consideration of all of the epidemiological and toxicological data, as well as all of the supporting data, e.g., toxicokinetics and cytogenetic data. Only through an integrated approach in which all such data are considered can scientifically defensible conclusions be reached.

The NRC committee's review noted several instances where EPA did not conduct a scientifically supported weight-of-evidence analysis for lymphohemotopoietic cancers, and stated:

"Given the limitations of the epidemiologic studies (particularly uncertainties of exposure assessment, possible confounding by other pollutants, and reliance on mortality rather than incidence data), a clear statement and consistent use of the weight-of-evidence criteria would strengthen the conclusions." *(NRC 2011, p. 83)*

"As stated in EPA's cancer guidelines, EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence" (EPA 2005a, Section 1.3.3, p 1-11). Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version." *(NRC 2011, p. 84)*

Consideration of the Epidemiological Data

According to the NRC committee:

> ***"The draft IRIS assessment comprehensively presents studies available through late 2009 that evaluate formaldehyde exposure and risk of LHP cancers. The draft provides commentary on multiple studies that had negative and positive findings, cohorts that were the subject of multiple analyses or publications, and meta-analyses. The emphasis on studies of occupational cohorts is appropriate, given that they provide the most specific and detailed exposure assessment that can be applied in risk assessments. The committee is not aware of any important studies that are missing from the analysis, although several relevant studies have been published since the draft was released (for example, Andersen et al. 2010; Bachand et al. 2010; Lu et al. 2010; Schwilk et al. 2010)."*** ***(NRC 2011, p. 82)***

This is virtually the same body of epidemiological literature and data that the NTP has considered in its preparation of the 12th RoC and that was considered by the International Agency for Research on Cancer (IARC) in its abbreviated re-review of formaldehyde as part of Monograph 100. The epidemiological evidence does not support a causal association between formaldehyde exposure and any lymphohematopoietic cancer.

As noted above, important limitations in the available epidemiologic studies identified by the NRC committee include:

> ***"…uncertainties of exposure assessment, possible confounding by other pollutants, and reliance on mortality rather than incidence data."*** ***(NRC 2011, p. 83)***

For example, the most recent update of the National Cancer Institute (NCI) formaldehyde workers cohort (Beane Freeman et al. 2009) demonstrates no excesses of leukemia or myeloid leukemia deaths, even after the erroneous omission of 995 (erroneously reported as 1,006) deaths is considered. Except for use of the "ever peak" as the dose metric, various quantitative exposure metrics produced no clear or statistically significant associations, including more appropriate "cumulative" or "cumulative peak" exposure metrics. Given the lack of excess leukemia and myeloid leukemia in this study, any observed "dose-response" relationships must be interpreted with extreme caution.

EPA relied extensively upon a study of embalmers (Hauptmann et al. 2009), despite the study's significant limitations. Of primary concern to our team of expert epidemiologists was the fact that this study also demonstrates no excess of myeloid leukemia deaths (PMR=108, 95% CI 72-156) (Cole 2010). Other key weaknesses that we have identified in this study include: exposure surrogate information was obtained from next-of-kin, often pertaining to work practices many decades prior; and there were substantial differences between myeloid leukemia decedents and the comparison group, including decade first employed, length of employment and race – all of which are potential indicators of selection bias. Ironically, no differences were seen between estimated average formaldehyde exposure, time-weighted average (TWA) 8-hour exposure, and peak exposure estimates. All, or at least some, of those differences would be expected if a true exposure-disease relationship were present.

Other cohorts (Coggon et al. 2003) and case-control studies based on cancer incidence registry cases (e.g., Blair et al. 2001, Partanen et al. 1993) found no convincing associations between formaldehyde exposure and either leukemia or myeloid leukemia.

Overall, based on our extensive and detailed critical review of the primary epidemiological literature, the human studies do not support the finding of a causal association between formaldehyde exposure and leukemia, including myeloid leukemia. Combining data from the three largest and strongest cohort studies (Beane Freeman et al. 2009; Pinkerton et al. 2004; Coggon et al. 2003), there is no evidence whatsoever of an increased risk of leukemia, with 152 observed cases compared to 153 expected cases based on age- and gender-appropriate population rates. Further, those few studies reporting positive associations were subject to important methodological limitations, as noted above and recognized by the expert NRC committee. Therefore, due to the overall lack of association between formaldehyde and leukemia, and the inherent limitations of the few studies reporting "positive" findings, there is insufficient epidemiological evidence to validly draw causal conclusions.

Regarding the epidemiological evidence on formaldehyde exposure and nasopharyngeal cancer (NPC), our critical review and synthesis found little support for causation, with most studies demonstrating no increased risk. The only positive association was noted in Hauptmann et al. (2004), which was limited to an excess of NPC from one study plant. This cluster has been reanalyzed (Marsh et al., 2007a, b) and, as noted by the NRC committee, this:

> ***"…reanalysis…provides evidence that the excess of NPC might be explained by other employment in silver-smithing or other metal-working industries in Connecticut. However, there is no evidence from other studies that those industries are associated with an increased risk of NPC."*** ***(NRC 2011, pp. 62-63).***

Thus, the epidemiological evidence is insufficient to validly support the conclusion that there is a causal association between formaldehyde exposure and either leukemia, any other hematopoietic cancers, or nasopharyngeal cancer.

Consideration of the Toxicokinetic Data

The NRC committee considered the following:

- **Formaldehyde is an Endogenous Chemical**

  > ***"The committee concludes… that regardless of the methodologic issue related to breath analysis, formaldehyde is normally present at a few parts per billion in exhaled breath…"*** ***(NRC 2011, p. 23)***

  > ***"The committee concludes that formaldehyde is an endogenous compound and …emphasizes that the natural presence of various concentrations of formaldehyde in target tissues remains an important uncertainty with regard to assessment of the additional dose received by inhalation."*** ***(NRC 2011, p. 23)***

Several studies in the scientific literature (Moser et al. 2005; Cap et al. 2008; Wang et al. 2008) demonstrate wide variability (i.e., concentrations ranging from 0 to approximately 73 ppb) in exhaled formaldehyde, and they consistently demonstrate median concentrations of exhaled formaldehyde ranging from 1 to 10 ppb, regardless of method of evaluation.

- **The Fate of Inhaled Formaldehyde – Lack of Evidence of Transport Beyond the Portal of Entry**

  "Moreover, the committee concludes that the weight of evidence suggests that it is unlikely for formaldehyde to appear in the blood as an intact molecule, except perhaps after exposures at doses that are high enough to overwhelm the metabolic capability of the tissue at the site of entry. Thus, although many sensitive and selective investigative approaches have been used, systemic concentrations from inhaled formaldehyde are indistinguishable from endogenous background concentrations." ***(NRC 2011, p. 27)***

  "The committee also found that the more contemporary work performed by Lu et al. (2010) that examined formaldehyde-induced DNA adducts and DDX cross-links provided no direct evidence of systemic availability of inhaled formaldehyde." ***(NRC 2011, p. 26)***

Because formaldehyde is an endogenously present compound, it is important to differentiate the presence of levels that are due to normal metabolic processes, from levels that might be present as a result of exogenous exposure. A number of studies have applied sensitive methods to differentiate exogenous and endogenous levels of formaldehyde in tissues (Casanova-Schmitz et al. 1984; Lu et al. 2010; Lu et al. 2011; Moeller et al. 2011; Swenberg et al. 2011). Using appropriate labeling methods, the results of the Lu et al. (2010) study demonstrated that neither exogenously inhaled formaldehyde nor its metabolite, methanediol, reached sites distant from the portal of entry. Swenberg and colleagues (Lu et al. 2010, 2011; Moeller et al. 2011; Swenberg et al. 2011) found that no exogenous formaldehyde-induced DNA adducts were detected in any distant tissue in rats or monkeys, including the bone marrow; however, DNA adducts from endogenous formaldehyde were present in all tissues examined. Lu et al. (2010) concluded that the results do "not support the biological plausibility that inhaled formaldehyde also causes leukemia."

Consideration of the Genotoxicity/Cytogenicity Data

It is generally acknowledged, including by the NRC committee, that formaldehyde is genotoxic, and numerous studies have shown genotoxic effects in cells exposed *in vitro*. Further, although a number of studies also have shown positive cytogenetic effects in circulating blood lymphocytes in heavily-exposed workers, it is unlikely that these effects are relevant to a possible leukemogenic effect of formaldehyde, particularly at low exposure levels. As the NRC committee stated:

> ***"...the overall body of evidence suggests that inhaled formaldehyde has a cytogenetic effect that can be detected in peripheral (circulating) blood lymphocytes. However, the committee concludes that data are insufficient to conclude definitively that formaldehyde is causing***

cytogenetic effects at distant sites. …a mechanism that would explain the occurrence of cytogenetic effects in circulating blood cells has not been established." (NRC 2011, p. 4)

The NRC committee also stated:

"The committee acknowledges that the database on the cytogenetic effects of formaldehyde in humans is supportive of EPA's … conclusion, that the mutagenic action of formaldehyde is not restricted to tissues at the point of contact. However, available data are insufficient to support definitive conclusions on several key issues. First, exposure assessment in the relevant human studies was generally lacking, and the effects observed occurred in highly exposed workers. In the absence of understanding of the shape of the dose-response curve for cytogenetic changes at low doses, it is difficult to extrapolate the findings to environmental exposures. Second, the mechanism of cytogenetic effects in circulating blood cells is not established – an uncertainty that complicates the committee's ability to link exposure with effects at distant sites. That data gap is especially problematic given the growing body of evidence that formaldehyde is not available systemically in any reactive form." (NRC 2011, p. 29)

In addition to these limitations pointed out by the NRC committee, other questions arise as to the relevance of the reported genotoxicity of formaldehyde in circulating peripheral blood to the production of leukemia in humans. For example, the circulating blood lymphocytes in which cytogenetic effects have been detected are mature T-cells which, as illustrated by the committee's report in Figure 5-1 (NRC 2001, p. 8), are different from the cell types of origin of the hematopoietic cancers that have been putatively linked by EPA and the NTP to formaldehyde exposure. This is further discussed below.

Consideration of the Mode-of-Action Data

The hypothetical modes of action presented in the draft IRIS document and reviewed by the NRC committee include the following:

- **EPA suggested that there is a direct-acting, mutagenic mode of action in target cells in the bone marrow, leading to lymphohemotopoietic cancers.**

Although EPA has postulated a mutagenic mode of action for leukemia and other hematopoietic cancers, the evidence is very weak, particularly as it relates to low, environmental exposures. The NRC committee stated:

"Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures." (NRC 2011, p. 34)

The NRC committee concluded that a direct genotoxic effect is unlikely because:

> ***"…despite the use of sensitive and selective analytic methods that are capable of differentiating endogenous exposures from exogenous ones, numerous studies have demonstrated that systemic delivery of formaldehyde is unlikely at concentrations that do not overwhelm metabolism."*** ***(NRC 2011, p. 5)***

The toxicokinetic data do not support the transport of either formaldehyde or a metabolite from the portal of entry at environmentally relevant concentrations that would exceed or overwhelm the contribution from endogenous formaldehyde. Further, the studies by Swenberg and colleagues unequivocally demonstrate that exogenous formaldehyde does not result in an increase in any of the tissues measured above those in the unexposed animals, thus indicating that endogenously produced formaldehyde predominates (Lu et al. 2010; Moeller et al. 2011; Lu et al. 2011; Swenberg et al. 2011).

- **EPA suggested another mode of action in which hematopoietic cells in the nasal epithelium return to the bone marrow.**

The NRC committee considered this possibility as a potential mode of action for formaldehyde, and concluded:

> ***"As a result, EPA could only speculate that circulating hematopoietic stem cells that percolate through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for mutations and clastogenic effects that eventually result in lymphohemotopoietic cancers. Experimental evidence of [this] mechanism is lacking."*** ***(NRC 2011, p. 34)***

Another section of the NRC report discusses the possible involvement of NALT – nasal-associated lymphoid tissue. This tissue is in close proximity to the nasal mucosa. EPA suggests that cells in the NALT are close enough to the nasal epithelium to absorb inhaled formaldehyde, which could induce chromosome mutations, and that cytogenetic changes in blood cells are consistent with this. However, there is no evidence that this actually occurs with formaldehyde. Further, the NALT is a collection of B-lymphocytes in all stages of differentiation, the circulating blood cells in which cytogenetic changes have been detected are mature T-lymphocytes, and what occurs in these cells is not indicative of what may be happening in B-cells in the NALT or elsewhere. Based on current medical understanding, the only agents that have been incriminated as causes of leukemia in mature T-lymphocytes are the HTLV-1 virus and other human leukemia viruses.

Another hypothesis proposed by EPA is that stem cells can leave the bone marrow, circulate to the nasal epithelium in close enough proximity to absorb formaldehyde, and thereby be affected by gene or chromosomal mutation. EPA describes this hypothetical pathway for the induction of acute myeloid leukemia (AML), but there is no empirical evidence to support EPA's hypothesis. Further, although, this evidence is what the Zhang et al. (2010) paper claimed to demonstrate, Zhang et al. (2010) did not do so, for the multiple reasons stated in our numerous prior comments and critiques of this paper.

In particular, Zhang et al. (2010) did not study lymphocytes, but instead studied what they assumed to be myeloid precursor cells. In fact, as the NRC report states, there is no evidence anywhere that this pathway is operative. Although the NRC report states that bone marrow myeloid stem cells leave the marrow and circulate, there is no evidence that under homeostatic conditions in normal animals, these cells return to the bone marrow. The fact that the NRC committee does not cite the Zhang et al. (2010) study can reasonably be interpreted that the committee concluded that there are severe limitations in

this study. Therefore, although both EPA and the NTP relied on the Zhang et al. (2010) study as supporting a role for a clastogenic mechanism in the development of leukemia as a result of formaldehyde exposure[1], the NRC apparently did not.

Applicability of the NTP's RoC Listing Criteria to Formaldehyde

The National Toxicology Program ("NTP") is responsible for periodically publishing the Report on Carcinogens ("RoC"), which lists substances that the NTP has concluded to be carcinogenic based upon the NTP's hazard assessment of specific cancer types (or "endpoints"). To add a substance to the list, the NTP must conclude, for at least one type of cancer, that the substance meets either of two NTP-created criteria – i.e. that the substance either is "known" or is "reasonably anticipated" to be a human carcinogen. Further, each RoC may include updates of listing decisions for substances that were included in prior RoCs, where such updates involve either changing the criterion (e.g., from "reasonably anticipated" to "known") which the NTP previously concluded applies to a particular cancer type, or adding a new cancer type to the prior listing for that substance. In revising any listing, the NTP should carefully delineate the scientific rationale for its listing decisions by stating precisely which type(s) of cancer and which listing criteria provide the basis for each listing decision.

The NTP now is completing work on the 12th RoC, and publicly-available drafts of the 12th RoC indicate that the NTP intends to state that formaldehyde is known to be a human carcinogen "based on sufficient evidence of carcinogenicity from studies in humans and supporting studies on mechanisms of carcinogenesis." The draft NTP listing notes that "[c]ausality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia...."

Formaldehyde already is listed in prior RoCs, based upon NTP's conclusion in the past that formaldehyde is reasonably anticipated to be a human carcinogen because of limited evidence in humans of increased incidences of nasopharyngeal cancers in exposed workers, and an increased incidence of squamous cell carcinoma of the nasal cavity in rats exposed by inhalation. However, neither myeloid leukemia nor any other lymphohematopoetic cancer, have been cited in prior RoCs as a basis for the NTP's listing decision. Indeed, the 11th RoC includes the statement that "[t]he available epidemiological data did not show an excess risk for ... lymphatic, or hematopoietic cancers."

As noted, RoC scientific evaluations that form the basis for RoC listing decisions involve the NTP's performance of hazard assessments of particular substances with reference to specific cancer endpoints (e.g., bladder cancer, lung cancer, specific blood cancers). EPA's IRIS assessments are more comprehensive in their scope, in that they encompass both hazard and dose-response assessments, and include both cancer and non-cancer endpoints. However, this difference in scope does not differentiate

[1] As pointed out in a submission to the IRIS docket, by Richard D. Irons, MT, PhD, DABT, Michael J. Thirman, MD, Richard J. Albertini, MD, PhD, and Annette M. Shipp, PhD, the conclusions reached by Zhang et al. are based on outdated 30-year-old theories of leukemogenesis that are not supported by current scientific and medical knowledge. The Zhang et al. study suffers from fundamental biological misconceptions, methodological deficiencies and inaccuracies that render it unreliable and inappropriate as a basis to confirm or suggest a relationship between formaldehyde and AML or any other leukemia. Document ID: EPA-HQ-ORD-2010-0396-0030.2; available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2010-0396-0030.2

the EPA IRIS hazard assessments for particular cancer types from the NTP's RoC hazard assessments for those same cancer types. Rather, EPA's hazard assessment of a substance's possible relation to a type of cancer is fully relevant to NTP's hazard assessment of that same substance for that same cancer type. ***Specifically, both EPA's IRIS formaldehyde hazard assessment for lymphohematopoietic malignancies (including myeloid leukemia), and the NRC committee's review of EPA's assessment, are directly relevant to the NTP's formaldehyde hazard assessment for the same endpoints.***

EPA and the NTP have had available, reviewed and relied upon the same studies, reports and underlying data in conducting their respective hazard evaluations of the possible relationship between formaldehyde exposure and leukemia and other lymphohematopoietic malignancies. Further, a reasonable, responsible reading of the NRC report clearly shows that the NRC committee did not simply find that EPA only needs to perform a technical re-write of the Agency's draft IRIS assessment. Rather, the NRC's careful, critical evaluation of the information addressed in EPA's draft assessment formed the basis for the NRC's extensive findings and conclusions, as summarized in the preceding sections of this paper – especially those pertaining to the lack of a demonstrated causal relation between formaldehyde and leukemia.

Therefore, although the NRC committee did not conduct an independent review of the literature and reach its own opinions about what can be drawn from that literature, the NTP should not take this to mean that the NTP's prior conclusions stand unchallenged, or that the NTP may disregard the NRC committee's report and conclusions. *Quite the opposite:* ***The NRC committee's review of and conclusions concerning the draft EPA IRIS report are, with respect to lymphohematopoietic malignancies (including myeloid leukemia), directly applicable to the NTP's own review and conclusions – precisely because the draft EPA and NTP reports involve the same studies and data sets.***

As discussed above, the NRC committee was particularly critical of EPA's failure to perform a scientifically supported weight-of-evidence (also referred to by the NRC committee and others as "strength-of-evidence") analysis of the relevant human, animal and mode-of-action data pertaining to whether there is a causal association between formaldehyde exposure and lymphohematopoetic cancers (including myeloid leukemia). A well-conducted and documented weight- or strength-of-evidence analysis is a core, essential component in the performance of chemical hazard assessments, and is incorporated into governmental (including the NTP), academic and private-sector hazard-assessment protocols and guidelines (see, e.g., NRC 2011, pp. 118-119). As applied to the current 12th RoC assessment of formaldehyde, if the NTP does not perform a proper weight- or strength-of-evidence analysis, this would constitute a serious scientific shortcoming in the NTP's hazard assessment, and result in major deficiencies of the sort that the NRC committee found with respect to EPA's draft IRIS assessment.

The NTP's fundamental approach in assessing leukemia endpoints has been to (1) assert that the human data (concerning formaldehyde exposures) are overwhelmingly conclusive as to causality, (2) note that there are no animal data of relevance to a determination of causality, and (3) suggest a number of hypothetical, unsupported mode-of-action mechanisms by which inhaled formaldehyde theoretically could either reach bone marrow or cause mutations in circulating blood cells that return to the bone marrow. As discussed above, following its careful review of EPA's draft IRIS assessment, the NRC committee concluded that (1) the human studies and data as evaluated by EPA fall far short of supporting a finding of causality, (2) there are no relevant animal data, and (3) the full range of modes-

of-action presented by EPA are simply hypotheses (with many being contradicted by existing data). ***Thus, if the NTP performs a true weight- or strength-of-evidence analysis, the NTP must conclude that causality is neither demonstrated nor credible.***

The NTP's criterion for classifying a substance as a "known" carcinogen is somewhat different than the criteria used by other agencies (such as EPA, or the International Agency for Research on Cancer), in that only human studies are considered for RoC listing decisions. Thus, NTP's criterion is that, in order for the NTP to list a substance as "Known To Be [A] Human Carcinogen", the NTP must conclude that "[t]here is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the ... substance ... and human cancer."[2]

Existing studies in humans do not provide "sufficient evidence" of formaldehyde's carcinogenicity involving myeloid leukemia. Specifically, the NTP and EPA have reviewed and relied upon the same human studies, and those studies do not "indicate a causal relationship between exposure to [formaldehyde] and [myeloid leukemia]" (or any other leukemia or lymphohematopoietic malignancy). The discussions above concerning epidemiological data and weight of evidence fully support the conclusion that formaldehyde is not a "known" human leukemogen as that term is used in the RoC listing criteria.

Noting that EPA had comprehensively reviewed the epidemiological literature, the NRC committee stated that this body of evidence was limited by:

> ***"...uncertainties of exposure assessment, possible confounding by other pollutants, and reliance on mortality rather than incidence data...." (NRC 2011, p. 83).***

Our independent evaluation of the epidemiology literature fully supports this conclusion. Furthermore, we have noted in submissions to the NTP that none of the large industrial cohort studies (including the embalmers' death certificate study – Hauptmann et al. (2009) – see page 4, above) demonstrate any statistically significant excess of myeloid leukemia when the limitations of these studies are appropriately considered. With respect to myeloid leukemia – for which the NTP considered the epidemiological evidence to be the strongest – we find the human evidence to be completely inadequate, and certainly not "sufficient" as that term is used in the NTP listing criterion. **Thus, a causal relationship between formaldehyde exposure and myeloid leukemia is not scientifically credible.**

For the NTP to categorize a substance (which is not "known" to be a carcinogen) as "reasonably anticipated to be [a] human carcinogen", the NTP must conclude that existing data support any one of three findings, only the first of which is relevant to the possible relationship between formaldehyde and leukemia:[3]

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[2] The NTP states that such evidence from studies in humans "can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people."

[3] Of the other two findings, one requires sufficient animal evidence, while the other requires a compelling structural relationship to a class of RoC-listed substances. For formaldehyde, neither of those conditions is met with respect to myeloid leukemia or other lymphohematopoietic malignancies.

> "There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded."

For the same reasons (discussed above) that existing human studies do not provide "sufficient evidence" of formaldehyde's carcinogenicity involving myeloid leukemia, those studies do not provide even "limited evidence" that formaldehyde is a leukemogen. Thus, the occasional positive associations reported in a few epidemiological studies do not reasonably constitute even "limited" evidence because of the limitations noted. To the contrary, the strongest well-conducted epidemiological studies demonstrate both no excess of myeloid leukemias, and no clear patterns with respect to various standard exposure metrics. Furthermore, the few sporadic positive associations reported are not unexpected due to chance. Therefore, the weight of epidemiological evidence is insufficient to support or even suggest a causal association.

Moreover, even if the epidemiological studies and data were stronger or more consistent such that they validly could be considered "limited" (which they cannot), the credibility of the causal association still is lacking. ***Specifically, the affirmative evidence against a plausible mode of action (discussed above) renders incredible – rather than credible (as that term is used in NTP's "reasonably-anticipated" listing criterion) – the hypothesis that formaldehyde causes myeloid leukemia or any other leukemia or lymphohematopoietic malignancy. Consequently, based upon a full, reasoned evaluation of the existing human studies, the NTP would not be justified in basing formaldehyde's listing in the 12th RoC as a "reasonably anticipated" carcinogen with respect to the myeloid leukemia endpoint.***

The NRC committee's review of the draft IRIS formaldehyde assessment agreed that the EPA criteria for causality were satisfied for formaldehyde and nasopharyngeal cancer (NPC) "on the basis of the combination of the epidemiologic findings with the experimental data and mechanistic data on formaldehyde" (NRC, 2011, p. 63). However, the epidemiological evidence alone was not sufficient and, based on the NTP listing criteria, would not satisfy the NTP's definition of a "known" human carcinogen.

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